I. ACTION SUMMARY

Claims 1-21 stand pending in the application. Claims 1, 2, 3, 4, 9, 10, 11, 12, 14, 16 and 18 stand rejected under 35 U.S.C. §102(b), second paragraph as being anticipated by Yurov et al. (Human Genetics (1996)). Claims 2 and 5 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yurov et al. (Human Genetics (1996)) in view of Drobniwski et al. (Journal of Clinical Microbiology, Jan. 2000). Claims 6 and 7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yurov et al. (Human Genetics (1996)) in view of Braissant et al. (Biochemica, 1998). Claims 2, 4, 8 and 21 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yurov et al. (Human Genetics (1996)) in view of Bresser et al. (US 5,225,326). Claims 13, 19 and 20 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yurov et al. (Human Genetics (1996)) in view of Ortiz et al. (Molecular and Cellular Probes, 1998). Claim 15 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Yurov et al. (Human Genetics (1996)) in view of Iris et al. (US 6,403,309). Claims 11, 12 and 17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yurov et al. (Human Genetics (1996)) in view of Hyldig-Nielsen (US 2001/0010910). No claim stands allowed.

II. FORMAL MATTERS

The Examiner is thanked for her return of the PTO-Form 1449 for the documents submitted with the last Office Action response. The Examiner is also thanked for taking the time to meet with Applicant's attorney, Brian Gildea, during the personal interview of April 7, 2004. A summary of that interview (in compliance with 37 C.F.R. § 1.133) is set forth below. The Examiner is invited to comment on Applicant's statement as set forth below under the heading "Interview Summary".

III. INTERVIEW SUMMARY

1. The interview focused on a discussion of Yurov et al., Hum. Genet (1996) 97: 390-398.
2. It was argued that Yurov et al. appears to teach at page 391, col. 1 under heading "Cell material" that all cells were fixed with methanol/acetic acid fixative and

then re-fixed before use. There does not appear to be any teaching of fixatives other than methanol/acetic acid in the Yurov reference.

3. The Examiner agreed with this interpretation of the Yurov et al. reference.

4. It was argued that the process for in situ-hybridization discussed by Yurov et al. at page 391, col. 2, first paragraph under the heading: "In situ hybridization and probe detection" **applies to all samples analyzed** including those described at page 391-392 bridging paragraphs under the heading: "Control of hybridization efficacy and specificity" wherein "In experiments when Cy3-labeled probes were hybridized separately or mixed with Cy5-, FluorX- or biotin-labeled probes, the step of microscope control for hybridization efficiency was performed without the detaching of coverslips and washing of slides."

5. The Examiner agreed with this interpretation of the Yurov et al. reference.

6. Accordingly, it was argued that process described by Yurov et al. at page 391, col. 2, first paragraph under the heading: "In situ hybridization and probe detection" specifically discloses the process of treating the cells with either of: 1) 0.07 N NaOH, 2 x SSC for 30 for chromosomal DNA denaturation; or 2) treatment with 2 N NaOH, 2 x SSC for 2-3 minutes without application of pronase or pepsin. Regardless, in each case the slides are dehydrated with an ethanol series **and air-dried**. It was further argued that this process, which involves washing with a NaOH solution followed by air-drying, would indisputably remove fixative from the cells and organisms and that all cells and organisms were treated Yurov et al. in this fashion. It was further argued that both methanol and acetic acid are volatile liquids that would, in addition to being washed away, evaporate during the air-drying step. It was argued that because it was agreed that the process described by Yurov et al. at page 391, col. 2, first paragraph under the heading: "In situ hybridization and probe detection" applies to all cells treated by Yurov et al. the process necessarily involves the separation of fixative from the cells.

7. It was argued that the discussion at page 391-391 bridging two paragraphs under the heading: "Control of hybridization efficacy and specificity" does not teach any modification of the process described by Yurov et al. at page 391, col. 2, first paragraph under the heading: "In situ hybridization and probe detection".

8. Whilst the Examiner agreed with the foregoing arguments (paragraphs 6 and 7 above), the Examiner argued degree of separation. Specifically, the Examiner argued that not all of the fixative had been separated and particularly that, in her opinion, residual fixative would remain inside the cells.
9. It was argued that fixation is a process that permeablizes cells so that reagents can enter into, and be washed out of, the cells. It was also pointed out that the procedure described by Yurov involved what is essentially a wash with a NaOH solution and that this was apparently applied to all cells processed by Yurov et al. Accordingly, it would be expected that at least some of the fixative would be separated from within the cells by operation of the processes described by Yurov et al. at page 391, col. 2, first paragraph under the heading: "In situ hybridization and probe detection".
10. Whilst the Examiner agreed with the foregoing arguments, the Examiner steadfastly argued that there was no evidence that all of the fixative was removed from the cells of Yurov et al.
11. It was argued that the present claims do not require that all of the fixative be separated from the cells or organisms.
12. The Examiner insisted that the rejection under 35 U.S.C. § 102(b) over Yurov et al. was still proper.
13. There was a discussion of possible ways the Yurov et al. reference might be overcome but no agreement could be reached.
14. Finally it was argued that the rejections under 35 U.S.C. § 103(a) were defective.
15. The Examiner maintained that the rejections under 35 U.S.C. § 103(a) were not defective.
16. The interview ended.

IV. RESPONSE TO THE OFFICE ACTION REJECTIONS

1. Rejection Under 35 U.S.C. § 102(b)

(a) Statement Of The Law Of 35 U.S.C. § 102(b)

It is well settled that to be anticipated, a prior art reference must teach each and every element/limitation of the claimed subject matter. M.P.E.P. § 2131. Moreover, the

elements must be arranged as required by the claim. *Id.* **"The identical invention must be shown in as complete detail as is contained in the claim"** *Id.* quoting from *Richardson v. Suzuki Motor Co.*, 868 F2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

(b) The Teachings Of Yurov et al. (Hum. Genet 97: 390-398 (1996))

Claim 1 recites: "... wherein the fixative agent or agents **and** excess molecular probe or probes are not separated from the organisms or cells prior to making the determination (emphasis added)." Claim 2-20 directly or indirectly depend from claim and thereby include this element/limitation.

In response to the Office Action dated March 25, 2003 Applicants argued that the Yurov et al. reference does not teach the separation of both fixative agents **and** excess probe or probes and thereby does not teach all of the elements of the claimed invention arranged as set forth in the claim. In the present Office Action (dated November 19, 2003) at page 4 under the section entitled: "Response To Arguments", the Examiner argued: "In response to applicant's first argument, that a "prior art reference must teach each and every element/limitation of the claimed subject matter" the examiner maintains that the Yurov et al. reference does just this." Specifically, the Examiner appears to rely heavily upon the text at the bottom of page 391 and continuing onto page 392 (page 391-392 bridging paragraphs under the heading: "Control of hybridization efficacy and specificity") arguing that the reference teaches "an embodiment of the Yurov method where the fixed cells with excess probe are viewed directly through the coverslip **before a washing step occurs** (emphasis added)." The implication from this statement appears to be that the Examiner views the absence of this wash step as being the evidence that" "the fixative agent or agents **and** excess molecular probe or probes are not separated from the organisms or cells prior to making the determination".

At the interview of April 7, 2004, the Examiner agreed that the discussion at page 391-391 bridging two paragraphs under the heading: "Control of hybridization efficacy and specificity" did not teach any modification of the process described by Yurov et al. at page 391, col. 2, first paragraph under the

heading: "In situ hybridization and probe detection". The Examiner further agreed that the process described by Yurov et al. at page 391, col. 2, first paragraph under the heading: "In situ hybridization and probe detection" applies to all cells treated by Yurov et al. Further, the process necessarily involves the separation of fixative from the cells with the stated caveat that the Examiner maintained that there was no evidence that the process **had removed all of the fixative agent or agents from the cells.**

Based upon the discussion occurring at the interview of April 7, 2004 is respectfully submitted that the Examiner has admitted that the Yurov et al. reference does not teach all of the elements/limitations of the claimed subject matter. In particular, it is respectfully submitted that present claims 1-20 directly or indirectly recite: "... wherein the fixative agent or agents **and** excess molecular probe or probes are not separated from the organisms or cells prior to making the determination (emphasis added)." Because the Examiner has admitted that the Yurov et al. reference necessarily discloses for all embodiments the separation of fixative from the cells, it cannot be reasonably argued that the fixative agent or agents and excess molecular probe or probes are not separated from the organisms or cells prior to making the determination.

In view of the foregoing, it is clear that Yurov et al. (Hum. Genet 97: 390-398 (1996)) does not anticipate the subject matter of independent claim 1, and its associated dependent claims, because this document simply does not teach all of the elements/limitations of the claimed subject matter arranged as required by the claims.

2. Rejections Under 35 U.S.C. § 103(a)

A. The Rejections Are Cumulative

All remaining rejections articulated in the present Office Action are made under 35 U.S.C. § 103(a) and are cumulative with respect to the rejection under 35 U.S.C. §102(b).[1] The Examiner relies upon arguments made in paragraph 1 of the Office Action with respect to the Yurov et al. (Hum. Genet 97: 390-398 (1996)) reference, the

[1] See paragraphs 2-7 of the Office Action dated November 19, 2003

accuracy of which Applicants dispute. Because all of these rejections necessarily rely upon an incorrect interpretation of the Yurov et al. reference with respect to the claimed subject matter, it is believed that all of the rejections under 35 U.S.C. §103(a) must properly be withdrawn.

B. The Rejection Based Upon Yurov et al. and Drobniewski et al.

(i) Statement Of The Rejection

At paragraph 2 of the Office Action dated November 19, 2003, the Examiner rejected claims 2 and 5 as being unpatenable over Yurov et al. in view of Drobniewski et al. (Journal of Clinical Microbiology (2000) 38(1): 444-447). The Examiner relies upon arguments made in paragraph 1 of the Office Action with respect to the Yurov et al. reference, the accuracy of which Applicants dispute. The Examiner appears to take the position that Yurov et al. does not teach various elements/limitations of the rejected claims but takes the position that Drobniewski et al. teach the missing element(s)/limitation(s).

(ii) The Rejection Is Defective

The rejection does not clearly identify any specific motivation to combine the references and further states no teaching or suggestion that would cause the ordinary practitioner to combine the two references. Accordingly, the rejection is defective. Indeed, it is believed that the combination of references is most definitely hindsight based and should properly be withdrawn.

(iii) The Reference Teaches A Separation Step

Finally, Applicants wish to point out that the reference teaches the operation of a separations step. In particular, at page 446, col. 1, lines 16-23 it is clear that Drobniewski et al. teach or suggest that the step of a final wash (a separation step) before visualization of the sample is to be performed. As discussed previously, Yurov et al. most definitely teach that a wash (a separation step) is to be performed after fixation. These references alone and in combination simply do not teach the absence of a separations step to remove either or both of fixative agents and/or excess probe.

Accordingly, there is no reasonable expectation of achieving the presently claimed subject matter and therefore the rejection should be withdrawn.

(iv) Argument Conclusion

For at least these reasons, it is respectfully submitted that the present rejection of claims 2 and 5 based upon the combination of Yurov et al. with Drobniewski et al. is improper under 35 U.S.C. § 103(a) and should be withdrawn.

C. *The Rejection Based Upon Yurov et al. and Braissant et al.*

(i) Statement Of The Rejection

At paragraph 3 of the Office Action dated November 19, 2003, the Examiner rejected claims 6 and 7 as being unpatenable over Yurov et al. in view of Braissant et al. (Biochemica (1998) 1: 10-15). The Examiner relies upon arguments made in paragraph 1 of the Office Action with respect to the Yurov et al. reference, the accuracy of which Applicants dispute. The Examiner appears to take the position that Yurov et al. does not teach various elements/limitations of the rejected claims but takes the position that Braissant et al. teach the missing element(s)/limitation(s).

(ii) The Rejection Is Defective

The rejection does not clearly identify any specific motivation to combine the references and further states no teaching or suggestion that would cause the ordinary practitioner to combine the two references. Accordingly, the rejection is defective. Indeed, it is believed that the combination of references is most definitely hindsight based and should properly be withdrawn.

(iii) The Reference Teaches A **Necessary** Separation Step

Finally, Applicants wish to point out that the reference teaches the **necessary** operation of a separations step. In particular, at page 13, col. 2, lines 11-16 the reference reads: "After hybridization, optimal washing conditions that ensure signal specificity consisted of rinses of 30 min in 2x SSC at room temperature, 1 h in 2 x SSC at 65°C, and 1 h in 0.1x SSC at 65°C." At page 15, col. 2, lines 11-13, the reference reads under the

heading "ISH protocol": "After hybridization, our washing procedure ensures signal specificity." At page 15, col. 2, lines 45-50 the reference reads: "After the removal of unspecific labeling in ethanol, a rapid rehydration step in water **was found to be necessary** in order to eliminate the tris precipitate from the tissue, which otherwise hampers histological observation. Taken together these statements by Braissant et al. demonstrate that a separation step is most definitely contemplated and even necessary in all of their embodiments. As discussed previously, Yurov et al. most definitely teach that a wash (a separation step) is to be performed after fixation. Consequently, these references alone and in combination simply do not teach the absence of a separations step to remove either or both of fixative agents and/or excess probe. Moreover, Braissant et al. is more appropriately viewed as a **teaching away** from the presently claimed subject matter. Accordingly, there is no reasonable expectation of achieving the presently claimed subject matter and therefore the rejection should be withdrawn.

(iv) Argument Conclusion

For at least these reasons, it is respectfully submitted that the present rejection of claims 6 and 7 based upon the combination of Yurov et al. with Braissant et al. is improper under 35 U.S.C. § 103(a) and should be withdrawn.

D. The Rejection Based Upon Yurov et al. and Bresser et al.

(i) Statement Of The Rejection

At paragraph 4 of the Office Action dated November 19, 2003, the Examiner rejected claims 2, 4, 8, and 21 as being unpatenable over Yurov et al. in view of Bresser et al. (US 5,225,326). The Examiner relies upon arguments made in paragraph 1 of the Office Action with respect to the Yurov et al. reference, the accuracy of which Applicants dispute. The Examiner appears to take the position that Yurov et al. does not teach various elements/limitations of the rejected claims but takes the position that Bresser et al. teach these elements/limitations.

(ii) The Rejection Is Defective